

# Herpes Simplex - A New Approach

RONNIE BORG  
MEDICAL STUDENT

**H**erpes viruses cause a wide spectrum of clinical conditions ranging from the cold sore to herpes encephalitis. They are characterised by their ability to take up permanent residence in the host, in a latent or quiescent state. Under certain circumstances the virus, which probably resides in the nerve ganglia, is reactivated and causes a recurrence of the clinical manifestations of infection.

Unlike bacteria, viruses are not free living organisms and are dependent upon the life processes of the cell to replicate. This close association between virus and cell inevitably resulted in antiviral agents causing unwanted effects on host cells, such as bone marrow suppression, teratogenicity and many other effects; thus confining the use of these agents to short-term topical application.

Wellcome's new product Acyclovir, previously known as *acyclo* *iguanosine*, is the first selective antiviral agent. The drug is active against the virus without exerting an effect upon the host cell by virtue of a two stage mechanism of action.

## 1. Selective concentration in infected cells.

This is the result of a) its conversion to the active form acyclovir tri-phosphate by a herpes virus enzyme - thymidine kinase. b) The active drug is not able to diffuse out of the cell and thus maintains an acyclovir concentration gradient within the cell. Host cell enzymes are unable to carry out this conversion to any significant extent, and so little or no active drug is formed in normal cells.

## 2. Inhibition of herpes DNA synthesis.

Deoxyguanosine tri-phosphate is incorporated into viral DNA and is a vital constituent for viral replication. Acyclovir tri-phosphate competes with deoxyguanosine tri-phosphate as a DNA polymerase substrate, but it cannot be incorporated into DNA in a way that will allow replication. Thus viral replication is inhibited.

Since acyclovir is activated only when the herpes simplex virus is present, it seals its own fate and normal cells are left unharmed. In fact it takes 3000 times more drug to affect normal cells than it does to inhibit the virus.

Whilst the ointment represents a significant advance in its particular area of use, the major impact of the drug is likely to be in other areas. By virtue of its lack of toxicity acyclovir may well be the first drug to enjoy widespread systemic use for treating herpes infections, although further work is needed. With intravenous acyclovir use transient renal impairment is seen as rises in plasma urea and serum creatinine levels. Acyclovir is relatively insoluble and largely excreted by the kidney, and it is possible that it is a recrystallization of the drug in the renal tubules which causes this effect. Care is therefore required in patients who are dehydrated or who have underlying renal disease, although no permanent kidney dysfunction has been seen. The results suggest that a more appropriate form of systemic therapy, such as oral or intramuscular administration, will provide significant benefit to patients suffering from herpes zoster infections.

Because of its low toxicity and high efficacy the results of early clinical trials have been received with enthusiasm.

"Acyclovir was found to be between 5 and 10 times active than cytarabine, idoxuridine and trifluorothymidine, and more than 100 times more active than vidarabine."

(J. Antimicrob. Chemother., (1979), 5, 431)

"The present paper reports the selectivity of action of a new class of antiviral agent that has extremely low toxicity for normal cells while having an inhibitory activity against HSV which is greater than that of any hitherto known compound."

(Proc. Natl. Acad. Sci. USA., (1977), 74/12, 5716)

"No adverse effects were seen with the acycloguanosine therapy."

(Jones, Bet al Lancet, (1979), 1, 243)

---

Condensed from an article in the *Postgraduate Medical Digest* No. 8 December 1981. Acyclovir is marketed by the Wellcome Foundation Ltd. under the name of Zovirax.

---